

SUMMARY OF DATA FOR CHEMICAL SELECTION

Black cohosh 84776-26-1

BASIS OF NOMINATION TO THE CSWG

Black cohosh is presented to the CSWG as part of a review of botanicals being used as dietary supplements in the United States. Despite a previous FDA classification of black cohosh as a medicinal herb of undefined safety, deregulation brought about by the 1994 Dietary Supplement Health and Education Act now permits this substance to be marketed to women who want to use it to treat menstrual and menopausal symptoms.

Many of the studies on the safety and efficacy of black cohosh have been conducted on Remifemin™, a popular German phytomedicine that is an alcoholic extract of black cohosh. Published reports contain few experimental details, making an independent assessment of the toxicity of black cohosh difficult. Overall, black cohosh extracts appear to affect luteinizing hormone secretion, although demonstrations of estrogenic/antiestrogenic activity are inconclusive. The combined effects of black cohosh and hormone replacement therapy are unknown. The presence of an active ingredient that influences blood pressure is a further concern.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee (ITC), Environmental Protection Agency (EPA), indicated that the ITC has deferred action on black cohosh.

Ms. Kara Dinda, Director of Education at the American Botanical Society, indicated that an expanded report on black cohosh will be included in a revised Commission E Monograph due to be released December 1999.

SELECTION STATUS

ACTION BY CSWG: 12/16/99

Studies requested:

Subchronic study (90-day) focusing on reproductive toxicity

Submit for testing to EPA's Endocrine Disruption Program

Priority: High

Rationale/Remarks:

Long history of use for treatment of menstrual and menopausal symptoms in women

Proprietary product with substantial worldwide use recently introduced in the United States

Binds to estrogen receptors and causes luteinizing hormone suppression

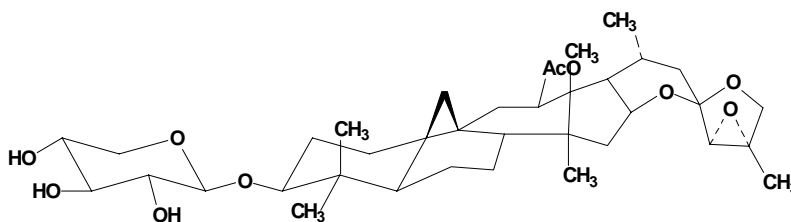
No chronic studies in humans or animals demonstrating the safety of black cohosh identified in the published literature

CSWG suggested that epidemiological studies on menopausal women who have taken black cohosh might be conducted

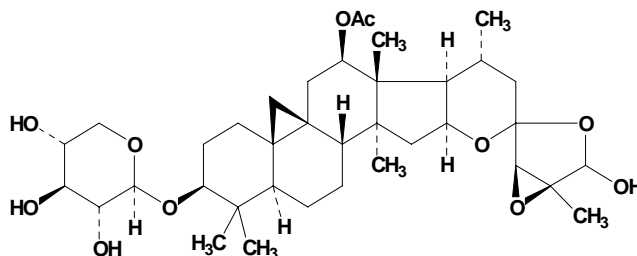
CHEMICAL IDENTIFICATION

<u>CAS Registry Number:</u>	84776-26-1
<u>Chemical Abstracts Service Name:</u>	<i>Cimicifuga racemosa</i> extract
<u>Botanical Name:</u>	<i>Cimicifuga racemosa</i> (L.) Nutt., family Ranunculaceae
<u>Synonyms and Trade Names:</u>	Actaea; black cohosh; black snake root; rattleroot, rattleweed; squaw root; bugbane; cimicifuga; richweed; Remifemin [™] (Budavari, 1997; Foster & Tyler, 1999)
<u>Structural Class:</u>	Botanical mixture; some pharmacologically active ingredients include triterpene glycosides (actein, 27-deoxyactein) and flavonoids (formononetin) (Berger <i>et al.</i> , 1988; Budavari, 1997; PDR Herbal, 1998)

Description: Black cohosh (*Cimicifuga racemosa*) is a tall perennial with a woody rootstock, smooth stem, and broadly ovate leaves, divided into 3-lobed leaflets with toothed margins. The plant can grow to 9 feet and has multiple white flowers that develop in midsummer. The medicinal part consists of the rhizome with attached roots. Nearly odorless, its black roots contain 15 to 20 percent of an amorphous resinous substance, cimicifugin, and a bitter principle, racemosin. The naturally occurring triterpene constituents of black cohosh include actein; cimigenol (16,23:16,24-diepoxy-9,19-cyclo-9 β -lanostane-3 β ,15 α ,25-triol); cimicifugioside; and 27-deoxyacetylacetol and its glycoside, 27-deoxyactein (27-deoxyacetylacetol-*O*- β -D-xylopyranoside). The flavonoid constituents

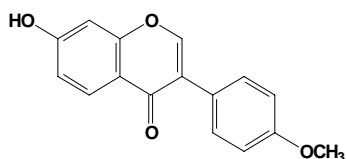


27-Deoxyactein

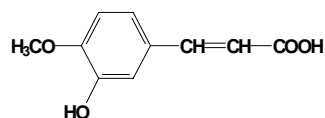


Actein (CAS No. 18642-44-9)

include formononetin (7-hydroxy-4'-methoxyisoflavone) and the aromatic constituents include isoferulic and salicylic acids (Duke, 1985; Berger *et al.*, 1988; Castelman, 1991; Bown, 1995; Lieberman, 1998; PDR Herbal, 1998; Schulz *et al.*, 1998; Duke & Beckstrom-Sternberg, 1999; Foster & Tyler, 1999).



Formononetin (CAS No. 485-72-3)



Isoferulic acid (CAS No. 537-73-5)

Technical Products and Impurities: Black cohosh is available at health food stores and pharmacies and through direct-mail companies, especially under the trade name Remifemin™ (ethanol extract of black cohosh standardized to contain 1 mg of triterpenes calculated as 27-deoxyactein per tablet). Extracts are sold as capsules, tablets, and liquids. Black cohosh may be sold as the sole ingredient in products or in combination nutraceuticals, which contain a variety of herbs and/or vitamins (Murray & Pizzorno, 1998; Anon., 1999a; Drug Emporium, 1999; Natrol, 1999; TFN, 1999; VitaminUSA, 1999).

EXPOSURE INFORMATION

Production and Producers: Preparations of black cohosh consist of the fresh or dried roots and rhizome of *Cimicifuga racemosa* (Budavari, 1997; Blumenthal, 1998). The roots are straight and dark brown. When cut, the interior of the roots has the appearance of off-white, porous wood. The rhizomes are harvested in autumn and used fresh in tinctures, or dried for use in decoctions, liquid extracts, and tinctures (Hobbs, 1998).

According to recent chemical catalogs and directories, black cohosh extract is manufactured or distributed by AIDP, Inc., Charles Bowman & Co., and Pharmline, Inc. Black cohosh is available from Acta Pharmacal, CPB International, Inc., DNP International Co., Inc., Extractsplus, Ital Nutrition, Inc., Kaltron/Pettibone, Madis Botanicals, Inc., Marc Development Corp., Maypro Industries, Inc., Mini Star International, Inc., QBI (Quality Botanical Ingredients), Inc., and Whole Herb Co. Black cohosh powder extract is available from Flavine International, Inc. (McCoy, 1998). Remifemin™ is manufactured by Schaper, Brümmer, Salzgitter in Germany (Lieberman, 1998)

No data were reported for black cohosh by the US International Trade Commission (USITC) in the ten most recent volumes of *Synthetic Organic Chemicals, US Production and Sales*, for the years 1984-1993. This source is no longer published.

In the 9-month period from May 1998 to February 1999, the Port Import/Export Reporting Service (PIERS) reported black cohosh extract powder and black cohosh powder imports of 2,380 and 23,505 pounds, respectively (Dialog Information Services, 1999).

Use Pattern: Black cohosh is indicated for various conditions including symptoms associated with premenstrual syndrome (PMS), dysmenorrhea, and menopause. It has been used for bronchial infections, labor and postpartum pains, sciatica, tinnitus, and arthritic and rheumatic diseases. Black cohosh is used in homeopathy for discomfort in late pregnancy, headaches, and depression, as well as for labor pains. The effective daily dose of black

cohosh, administered orally, is 40 mg (Bown, 1995; Tyler, 1997; PDR Herbal, 1998; Schoenberger, 1998).

Black cohosh was first used by Native Americans who boiled the root in water and drank the resulting beverage for a variety of conditions, including fatigue, arthritis, sore throat, and rattlesnake bite - hence the name “snakeroot.” Native Americans also called black cohosh “squawroot” because of its predominant uses to treat female menstrual complaints, to relieve pregnancy-related pain or distress, and to promote uncomplicated delivery and quick recovery (Castelman, 1991; Lieberman, 1998; Foster & Tyler, 1999).

A popular 19th century patent medicine, Lydia E. Pinkham’s Vegetable Compound was introduced in 1876 to treat menstrual cramps. For years the activity of Vegetable Compound was attributed to the effects of its 36-proof alcohol. A detailed review of the formula, however, shows that three teaspoons a day yielded slightly more than the now-recommended therapeutic dose of black cohosh (Castelman, 1991; Tyler, 1997).

In Germany, black cohosh has been used since the early 1940s as a natural agent for treating PMS, dysmenorrhea, and menopause, and it remains a popular natural alternative to estrogen therapy. Since 1956, more than 6.5 million menopausal women in Germany have used Remifemin™. Although black cohosh remains an unapproved drug in the US, it is now widely available as a dietary supplement (Tyler, 1997; Hobbs, 1998; Lieberman, 1998; *Anon.*, 1999b).

Beginning in the 1960s, published results of European clinical trials have described the effectiveness of black cohosh in treating menstrual and menopausal ailments. Since the 1980s, five clinical studies (none double-blinded) have compared Remifemin™ with placebo and/or estrogen replacement in the treatment of menopausal symptoms. The largest, an open, multicenter study with data on 629 patients collected by 131 general practitioners reported favorable results in 80 percent of patients after 6-8 weeks of treatment. Improvements included relief of hot flashes, sweating, headache, vertigo,

palpitation, and tinnitus (Lieberman, 1998; Liske, 1998; Foster & Tyler, 1999).

It has been reported that the use of Remifemin™ is not contraindicated in hormone-sensitive mammary carcinoma, hormone-sensitive endometrial carcinoma, malignant melanoma, or other conditions for which estrogen replacement is contraindicated (Lieberman, 1998). Others caution about taking black cohosh with other hormonal therapies since *C. racemosa* may interact with the sex hormone system (Wong *et al.*, 1998).

Human Exposure: In the US, women who use dietary supplements to treat menstrual and menopausal symptoms are the primary source of human exposure to black cohosh. Although overall figures for the use of black cohosh supplements in the US are not available, more than 10 million monthly units of Remifemin™ (packet of 60 tablets) were sold in 1997 (Lieberman, 1998; Murray & Pizzorno, 1998; Murray, 1999). According to PharmaPrint, a pharmaceutical company that is developing a black cohosh product, worldwide, there is a \$1.4 billion prescription drug market for treating menopausal symptoms (PharmaPrint, 1999).

The potential for worker exposure to black cohosh exists during the growing, harvesting and processing of the plants. For the purposes of quantifying the costs of food labeling regulations, the US Food and Drug Administration (FDA) (1997) estimated that there were 250 herbal/botanical firms; the number of firms producing black cohosh products was not identified. No listing was found for black cohosh in the National Occupational Exposure Survey (NOES), which was conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983.

Environmental Occurrence: Black cohosh, a member of the *Ranunculaceae* family, is a North American species of *Cimicifuga* found in rich, open woodlands. Abundant in some eastern states, it grows from the Midwest to New England. The plant will grow well in gardens almost anywhere in the US, whether in full sun or complete shade (Beuscher, 1995; Hobbs,

1998).

Regulatory Status: Since 1994, dietary supplements in the United States have been regulated under the Dietary Supplement Health and Education Act (DSHEA). For dietary supplements on the market before October 15, 1994, the DSHEA requires no proof of safety in order for them to remain on the market. The labeling requirements for supplements allow warnings and dosage recommendations as well as substantiated “structure or function” claims. All claims must prominently note that they have not been evaluated by the FDA, and bear the statement “This product is not intended to diagnose, treat, cure, or prevent any disease” (Croom & Walker, 1995). Thus, dietary supplements containing black cohosh could not claim to treat PMS or menopausal symptoms.

The Bundesgesundheitsamt (the Federal Health Agency, now called the Federal Institute for Drugs and Medical Devices), the German equivalent to the FDA in the United States, lists no contraindications or limitations of use for black cohosh, however, black cohosh is subject to legal restrictions in some countries. In the US, the FDA classified black cohosh as a medicinal herb of undefined safety with no pharmacologic evidence of any therapeutic value (Duke, 1985; Murray & Pizzorno, 1998).

In 1978, the Bundesgesundheitsamt established an expert committee on herbal remedies to evaluate the safety and efficacy of phytomedicines. The assessments of this so-called “Commission E” are independent of the Bundesgesundheitsamt. Commission E recommended black cohosh for treating PMS, menstrual cramps, and menopausal symptoms. Although Commission E recommends a duration of administration of 6 months or less, historically black cohosh has been used for longer periods (Blumenthal, 1998; Lieberman, 1998).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to black cohosh and cancer risks in humans were identified in the available literature.

An intake of black cohosh at very high dosages (5 g of drug or 12 g of extract) leads to vomiting, headache, dizziness, limb pains, and lowered blood pressure. Overdosing during pregnancy can cause premature birth (Duke, 1985; Tyler, 1997; PDR Herbal, 1998).

As of October 20, 1998, the FDA Special Nutritionals Adverse Event Monitoring System listed eight matches for products containing black cohosh in eight adverse event reports. Adverse events included heart attack; flushing of skin, swelling, and headache; blood count abnormalities; anxiety; headaches, blurred vision, dizziness; diarrhea, weakness, nephrotic syndrome; chest pain; and headaches and high blood pressure. There is no certainty that a reported adverse event can be attributed to a particular product or ingredient (FDA, 1998).

The largest clinical trial of black cohosh conducted to date was an open study involving 131 doctors and 629 female patients. Seven percent of the patients reported side effects but none discontinued therapy (Lieberman, 1998; Foster & Tyler, 1999). This study was of short duration, a matter of weeks; no studies that would permit a comparison of the long-term benefits and risks of postmenopausal administration of black cohosh vs. hormone treatment were identified in the available literature. None of the studies conducted on black cohosh to date has provided information relevant to the evaluation of cancerous or precancerous lesions.

Animal Data: No 2-year carcinogenicity studies of black cohosh in animals were identified in the available literature.

In a six-month chronic toxicity study of Remifemin™ in rats, few clinical or

histopathologically relevant observations were made. At 1.8 g/kg body weight, roughly ninety times the therapeutic dose, no effects were reported; at 5 g/kg, weight loss was the only observation (Beuscher, 1995; Murray & Pizzorno, 1998; Foster & Tyler, 1999). No details of this study, apparently conducted for the manufacturer, were available for review.

The minimal lethal dose of black cohosh extract was reported to be >500 mg/kg (po) for the mouse, >1000 mg/kg (po) for the rat, and >70 mg/kg for the rabbit. With application for 30 days, the minimum lethal dose in rabbits was >6 mg/kg (po) and for the mouse it was >10 mg/kg (ip) (Beuscher, 1995).

Short-Term Tests: Black cohosh was described as negative for mutagenicity in the Ames *Salmonella* assay (Beuscher, 1995). No information on study design or details of the experiment were reported in the available literature.

Metabolism: No information was found in the available literature.

Other Biological Effects: *Luteinizing hormone suppression and the estrogen receptor.* The endocrine effects of black cohosh extracts, which presumably are exerted on the pituitary, have been investigated *in vitro*, in ovariectomized rats, and in patients with menopausal complaints. The putative action of black cohosh is on the gonadotropin system, through estrogen ligands that suppress luteinizing hormone (LH) release, and through nonestrogen ligands that appear to decrease LH secretion with long-term use (Wong *et al.*, 1998).

Cessation of ovarian function during menopause is characterized by reduced estrogen production and increased LH and follicle stimulating hormone (FSH) secretion. An open, controlled comparative study of 110 patients who complained of climacteric symptoms demonstrated significant LH suppression in the Remifemin™ group compared with placebo. No significant effect on FSH serum concentration was observed in either group after two months of treatment. The authors noted that the selective suppression of black cohosh extracts on LH but not FSH secretion in menopausal women was consistent with

prior studies in ovariectomized rats (Düker *et al.*, 1991).

Düker and coworkers (1991) then attempted to concentrate the active compounds by extracting Remifemin™ with chloroform. The hydrophilic extract did not suppress LH secretion in ovariectomized rats, but the lipophilic extract exerted a strong LH suppressive effect. Further purification of the lipophilic fraction resulted in eight fractions which were analyzed for LH suppression and for their ability to bind to estrogen receptors. One fraction significantly inhibited LH secretion but was not active in the estrogen receptor binding assay, two fractions were active in both assays, and the most potent fraction in terms of estrogen receptor binding did not affect LH secretion. The authors concluded that the effects seen in menopausal women and ovariectomized rats were caused by at least three different synergistically acting compounds.

Beuscher also attempted to characterize the active compounds in Remifemin™. The extract was especially rich in formononetin, a competitive ligand in the estrogen receptor assay. The formononetin fraction did not produce a change in serum LH levels. Because formononetin is known as the major estrogenic factor in soy, Beuscher's results have been interpreted to mean that black cohosh possesses some degree of estrogenic activity (Beuscher, 1995; Budavari, 1997; Foster & Tyler, 1999).

A study of 80 female patients administered Remifemin™ for 12 weeks is also cited as evidence of estrogenic activity. With the herbal extract, a notable increase in the degree of proliferation of the vaginal epithelium was reported. Conjugated estrogens, given as a positive control, influenced the vaginal epithelium only slightly (Stoll, 1987; Lieberman, 1998).

In contrast to the previously cited studies, Einer-Jensen and coworkers (1996) found no evidence of an estrogenic effect when a 50 percent water/ethanol extract of *Cimicifuga* was administered at 6-600 mg/kg orally for 3 days to groups of 10 immature mice and uterine weight was measured. Similarly, 6-600 mg/kg *Cimicifuga* injected subcutaneously

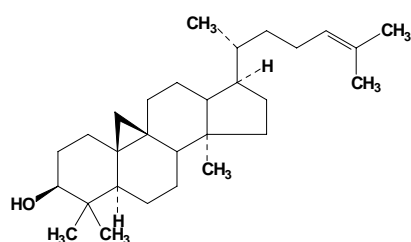
(sc) to groups of 12 ovariectomized rats for 3 days did not result in cornified cells when vaginal smears were investigated. The authors postulated that although *Cimicifuga* does not contain estrogens in the traditional sense, it may contain substances that interfere with the regulation of the pituitary-gonad axes, perhaps through competitive inhibition at the hypothalamic-pituitary level.

Potential effects on breast cancer. Researchers have sought to determine whether *Cimicifuga* extract stimulates the growth of estrogen-dependent breast tumor cells *in vitro*. These *in vitro* studies have shown no stimulatory effects, in fact, the effects were described as being inhibitory. Furthermore, the combination of Remifemin™ with tamoxifen has been shown to potentiate the effects of tamoxifen (Murray & Pizzorno, 1998).

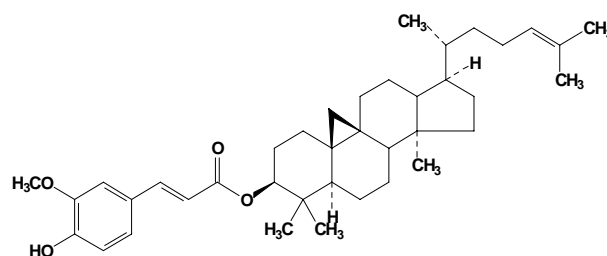
Teratogenicity. According to Foster and Tyler (1999), studies of black cohosh for teratogenicity were negative. No experimental details were provided.

Heart. Actein, a steroidal triterpene derivative present in black cohosh, was found to lower blood pressure in rabbits and cats but not in dogs (Foster & Tyler, 1999). Black cohosh overdoses may cause a depressed heart rate in susceptible individuals at relatively low doses (Castelman, 1991). These effects have led to the recommendation that anyone with heart disease should not use black cohosh (Castelman, 1991) and that patients taking medications to control high blood pressure should be cautioned about black cohosh because of the potential for an additive hypotensive effect (Schoenberger, 1998).

Structure Activity Relationships: Black cohosh consists of a complex mixture of natural products which does not lend itself to traditional structure activity analysis. No information adequate to judge the mutagenic or carcinogenic potential of black cohosh was found in the available literature.



Cycloartenol (CAS No. 469-38-5)



Cycloartenol ferulate (CAS No. 21238-33-5)

The highly oxygenated triterpene glycosides in black cohosh show close structural relationship to cycloartenol, a key intermediate in the biosynthesis of steroid glycosides in plants. Cycloartenol ferulate is used to treat symptoms associated with menopause (Berger *et al.*, 1988; Budavari, 1997). Yasukawa and coworkers (1998) reported that cycloartenol ferulate inhibited the tumor-promoting effect of 12-*o*-tetradecanoylphorbol-13-acetate (TPA) in 7,12-dimethylbenz[a]anthracene-initiated mice.

Table 1 lists the biological activities of individual components of black cohosh reported by Duke and Beckstrom-Sternberg (1999) in the US Department of Agriculture Phytochemical Database.

Table 1. Biological Activities of Individual Components of Black Cohosh

Chemicals	Concentration (ppm)	Health Effects
actein		hypotensive, vasodilator
cimicifugin	150,000-200,000 in root	no activities reported
cimigenol-xyloside		no activities reported
cimigoside		no activities reported
27-deoxyacetylacteol		no activities reported
formononetin		abortifacient, anticephalagic, antifeedant, cancer-preventive, estrogenic, fungicide, herbicide, hypocholesterolemic, hypolipidemic, myorelaxant, VAM-stimulant
isoferulic acid		antiedemic, anti-inflammatory, hypothermic
racemoside		antiulcer

References

- Anon. (1999a) *Black Cohosh*. [<http://www.unc.edu/~cebradsh/blackco.html>]
- Anon. (1999b) Black Cohosh. [<http://www.terraworld.net/sekmed/Medical%20A%20to%20B.htm>]
- Berger, S., Junior, P. & Kopanski, L. (1988) 27-Deoxyactein: a new polycyclic triterpenoid glycoside from *Actaea racemosa*. *Planta. Medica.*, 579
- Beuscher, N. (1995) *Cimicifuga racemosa* L. - Black cohosh. *Zeitschrift fur phytotherapie*, **16**, 301-310 [German]
- Blumenthal, M., ed. (1998) *The German Commission E Monographs*. American Botanical Council, Austin, TX, pp. ix, 90
- Bown, D. (1995) *Encyclopedia of Herbs & Their Uses*. The Herb Society of America, New York, NY, Dorling Kindersley Publishing, Inc., pp. 107-108
- Budavari, S., ed. (1997) *The Merck Index* (CD-ROM), Whitehouse Station, NJ, Merck & Co., Inc.
- Castelman, M. (1991) *The Healing Herbs*. Emmaus, PA., Rodale Press, pp. 75-78
- Croom, E.M., Jr. & Walker, L. (1995) Botanicals in the pharmacy: New life for old remedies. *Drug Top.*, **139**(6), 84-93
- Dialog Information Services (1999) *PIERS Imports (US Ports) (File 573)*, Palo Alto, CA, searched September, 1999 [Accession Nos. 05647316, 04772192, 08436963]
- Drug Emporium (1999) 21st Century Dietary Supplement, Black Cohosh Extract. [<http://www.drugemporium.com>]
- Duke, J.A. (1985) *CRC Handbook of Medicinal Herbs*. Boca Raton, FL, CRC Press, Inc., pp. 120-121
- Duke, J.A. & Beckstrom-Sternberg, S.M. (1999) Chemicals in: *Cimicifuga racemosa* (L.) NUTT. (Ranunculaceae) — Black cohosh. *Dr. Duke's Phytochemical and Ethnobotanical Databases*. [<http://www.ars-grin.gov/cgi-bin/duke/farmacy2.pl>]
- Düker, E., Kopanski, L., Jarry, H. & Wuttke, W. (1991) Effects of extracts from *Cimicifuga racemosa* on gonadotropin release in menopausal women and ovariectomized rats. *Planta. Medica.*, **57**, 420-424
- Einer-Jenson, N., Zhao, J., Anderson, K.P. & Kristofferson, K. (1996) *Cimicifuga* and *Melbrosia* lack

estrogenic effects in mice and rats. *Maturitas*, **25**, 149-153

FDA (1997) Food Labeling; Statement of Identity, Nutrition Labeling and Ingredient Labeling of Dietary Supplements; Compliance Policy Guide, Revocation. *Fed. Regist.*, **62**(184), 49825-49858

FDA (1998) *The SN/AEMS Web Report Search Results for Black Cohosh*, US Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Special Nutritionals, October 20, 1998 [<http://www.vm.cfsan.fda.gov/cgi-bin/aems.cgi>]

Foster, S. & Tyler, V.E. (1999) *Tyler's Honest Herbal. A Sensible Guide to the use of Herbs and Related Remedies*, 4th edition, Binghamton, NY, The Haworth Press, pp. 51-53

Hobbs, C. (1998) *Black Cohosh*. [<http://207.36.93.123/fp/blackcohosh.html>]

Lieberman, S. (1998) A review of the effectiveness of *Cimicifuga racemosa* (black cohosh) for the symptoms of menopause. *J. Women's Health*, **7**(5), 525-529

Liske, E. (1998) Therapeutic efficacy and safety of *Cimicifuga racemosa* for gynecologic disorders. *Advances in Therapy*, **15**, 45-52 [Abstract]

McCoy, M., ed. (1998) *OPD 1998 Chemical Buyers Directory*, 85th ed., New York, Schnell Publishing Co., p. 159

Murray, M. (1999) Black cohosh - cimicifuga extract - A natural alternative to estrogen for menopause. [<http://www.totalhealthdiscount.com/blkcohs.html>]

Murray, M. & Pizzorno, J. (1998) *The Encyclopedia of Natural Medicine*. Rocklin, CA., Prima Publishing, pp. 639-641.

Natrol (1999) Natrol for Women - Hot Flashex. [<http://www.where2getit.com/natrol/>]

NLM (1999) *ChemID*, Bethesda, MD, searched September, 1999 [Record No. 84776-26-1]

PharmaPrint (1999) Pharmaceutical market. [<http://www.pharmaprint.com/market.htm>]

PDR Herbal (1998) *Physician's Desk Reference for Herbal Medicines*, Montvale, New Jersey, Medical Economics Data Production Co., pp. 746-747

Schoenberger, C. (1998) Materia Medica. *Carolina J. Pharm.*, **78**(May-June), 14-15

Schulz, V., Hansel, R. & Tyler, V.E. (1998) *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine*, 3rd edition. Springer, Berlin, pp. 243-244

Stoll, W. (1987) Phytotherapy influences atrophic vaginal epithelium. *Therapeutikon*, **1**, 23 [German]

[cited in Lieberman, 1998]

TFN (1999) *Remifemin*TM. [<http://www.tfnutrition.com/sportsnutrition/08556.html>]

Tyler, V.E. (1997) *The bright side of black cohosh*. [<http://207.36.93.123/fp/cohosh.html>]

VitaminUSA (1999) *Black Cohosh (Cimifuga racemosa)*. [<http://pharmacy.stores.yahoo.com/pharmacy/00-33984-04111.html>]

Wong, A.H., Smith, M. & Boon, H.S. (1998) Herbal remedies in psychiatric practice. *Arch. Gen. Psychiatry*, **55**, 1033-1044

Yasukawa, K., Akihisa, T., Kimura, Y., Tamura, T. & Takido, M. (1998) Inhibitory effects of cycloartenol ferulate, a component of rice bran, on tumor promotion in two-stage carcinogenesis in mouse skin. *Biol. Pharm. Bull.*, **21**(10), 1072-1076 [Abstract]